

1 RECORD OF ORAL HEARING  
2  
3 UNITED STATES PATENT AND TRADEMARK OFFICE  
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5  
6 BEFORE THE BOARD OF PATENT APPEALS  
7 AND INTERFERENCES  
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10 Ex parte GEORGE H. YOO  
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13 Appeal 2007-2864  
14 Application 10/747,798  
15 Technology Center 1600  
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18 Oral Hearing Held: Wednesday, September 12, 2007  
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22 Before ERIC GRIMES, LORA M. GREEN, and  
23 RICHARD M. LEOVITZ, Administrative Patent Judges  
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26 ON BEHALF OF THE APPELLANTS:  
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1 Appeal 2007-2864  
2 Application 10/747,798

1 The above-entitled matter came on for hearing on Wednesday,  
2 September 12, 2007, commencing at 1:45 p.m., at the U.S. Patent and  
3 Trademark Office, 600 Dulany Street, 9th Floor, Hearing Room A,  
4 Alexandria, Virginia, before Jan M. Jablonsky, Notary Public.

5 JUDGE GRIMES: Good afternoon, Ms. De La Paz.

6 As you may know, you'll have 20 minutes to present your  
7 arguments, and we do have a lot of cases this afternoon, so we're going to  
8 have to stick pretty closely to that 20 minutes. Start whenever you're ready.

9 MS. DE LA PAZ: Good afternoon, Your Honors.

10 The subject matter of the present invention that's under  
11 consideration today pertains to methods of inhibiting the growth of a  
12 papillomavirus. The methods involve topically applying to lesions that  
13 include papillomavirus infected cell, a composition that includes an  
14 expression cassette that includes a promoter, operably coupled to a  
15 gene-encoding p53.

16 Now, there are rejections of two types that are involved in this  
17 appeal. First, there are four rejections under Section 102 and two rejections  
18 under Section 103. The main issue in this appeal is whether the claims are  
19 inherently anticipated by any of the Clayman references, the recombinant  
20 advisory committee meeting minutes or the Nielsen reference. Taking these  
21 one-by-one, the Clayman reference is a research protocol of Clayman which  
22 describes a proposal to administer by intramucosal injection a composition  
23 that includes Adenovirus Ad-p53 into the lesions, followed by swishing of  
24 the lesions in the mouth.

25 The Recombinant Advisory Committee meeting minutes, which  
26 I'll just abbreviate -- the RAC meeting minutes is meeting minutes from the

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7 Appeal 2007-2864  
8 Application 10/747,798

1 Committee of the National Institutes of Health in Clayman describing his  
2 own particular invention pertaining to that was set forth in the Clayman  
3 reference, namely intramucosal injection of ADP53 followed by oral  
4 swishes. Nielsen is a published PCT application which describes  
5 combination p-53 plus gemcitabine to treat cervical and head and neck  
6 cancers. None of these references, either Clayman, the RAC meeting  
7 minutes, or Nielsen expressly set forth any information regarding any  
8 papillomavirus infection of any cell in any lesion.

9               Now, the Examiner pulls in two additional references to make  
10 his case for inherent anticipation. The Oda reference is a study which  
11 describes in its background section a study wherein, in a sample of patients  
12 with oral carcinoma, up to 90 percent had HPV DNA in the lesions. The  
13 Flaitz reference, which he also cites as supporting inherent anticipation, cites  
14 to a study of oral pre-malignancies for up to 42 percent of the lesions had  
15 HPV-infected DNA.

16               So, basically, the Examiner concludes that there must be  
17 inherent anticipation because Oda inflates teach that in some patients there's  
18 HPV infection. However, the Examiner applies an incorrect standard for  
19 determining an inherent anticipation. I direct you to a Federal Circuit case  
20 from 1991, Continental Can Company v. Monsanto. And I quote: "To serve  
21 as an anticipation when the reference is silent about the asserted inherent  
22 characteristic, such gap in the reference may be filled with recourse to  
23 extrinsic evidence that such evidence must make clear that the missing  
24 descriptive subject matter is necessarily present in the thing described in the  
25 reference and that it would be so recognized by persons of ordinary skill in  
26 the art. Here, the Examiner has not shown that any of the lesions that would

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13 Appeal 2007-2864  
14 Application 10/747,798

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1 have been treated in Clayman, the RAC minutes, or Nielsen necessarily  
2 included HPV-infected cells.

3 JUDGE GREEN: I'm sorry.

4 JUDGE GRIMES: Go ahead.

5 JUDGE GREEN: Don't Oda and Flaitz show that if you treat  
6 100 patients, one of ordinary skill in the art would have expected at least 42  
7 to have HPV? So, what you're saying, to me -- it seems to me that you're  
8 arguing unless Oda and Flaitz, say, HPV is involved in 100 percent of these  
9 lesions, you can't have any anticipation.

10 MS. DE LA PAZ: Well, another study we cited in the  
11 background section of the specification is Gilson, and that was made of  
12 record in the IDS that C39. In that study, they looked at a sample of patients  
13 of newly diagnosed carcinoma and found 25 percent of patients had  
14 papilloma-positive DNA. So, how much is too much?

15 JUDGE GREEN: But even if he has 25 out of 100, at least in  
16 that 25, I mean, HPV is known to be involved in these types of lesions. And  
17 that seems to me something that the Examiner established is well-known in  
18 this particular art.

19 MS. DE LA PAZ: Well, he may have established there may be  
20 some association, but let's look again. Here's another case from the Fed  
21 Circuit -- Mehl/Biophile v. Milgraum. That's a Federal Circuit case from  
22 1999. In that case, the claims recited directing a laser in a vertical direction  
23 towards a hair follicle. In the prior art that was cited as inherently  
24 anticipating the reference involved directing a laser at tattoo pigment on a  
25 skin lesion. And the argument was, well, there's inherent anticipation,  
26 because one could have vertically aligned the laser with a hair follicle that

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19 Appeal 2007-2864  
20 Application 10/747,798

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1 might have been in the region of the tattoo pigment. And the Federal Circuit  
2 said no, the mere possibility that such an alignment does not legally suffice  
3 to show anticipation and that occasional results are not inherent. So,  
4 occasional results are not inherent.

5 JUDGE GREEN: This is a different case because you don't  
6 have a possibility that even using your number, 25 percent, if you treat 100  
7 patients, you have a probability, not a possibility that 25 of those 100  
8 patients are going to have the HPV involvement.

9 MS. DE LA PAZ: Well, a possibility is a possibility. It's very  
10 possible that none of those patients could have HPV involvement in any of  
11 those studies.

12 JUDGE LEBOVITZ: Clayton actually looked at the HPV  
13 status of the patient, and doesn't that establish that he knew that a certain  
14 fraction of those patients were going to be HPV-positive?

15 MS. DE LA PAZ: Well, he looked at a fraction of patients, but  
16 again, the standard for inherent anticipation is whether the limitation is  
17 necessarily present. They may not be present.

18 JUDGE LEBOVITZ: What about Perricone ,where they were  
19 putting vitamin C on the face to protect against sunburn? Not all people  
20 who put it on were going to go out and get into the sun, but the fact is the  
21 population was susceptible to sunburn. So, in the same way, you know that  
22 the population of people that are being treated by Clayman, a certain percent  
23 will actually have the HPV-positive.

24 MS. DE LA PAZ: Well, I disagree. The fact is, you don't  
25 know that the population that will be treated by Clayman will definitely have  
26 HPV-infected cells. It's possible they may not.

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25 Appeal 2007-2864  
26 Application 10/747,798

1 JUDGE GREEN: So you want 100 percent certainty?

2 MS. DE LA PAZ: Well, a range in these studies from 25  
3 percent to 42 percent to 90 percent shows at least that there's a lot of  
4 variability among those studies, and it's not unreasonable to B

5 JUDGE GREEN: But even if we take the lowest range, 25  
6 percent, there is a correlation marked that HPV is involved in these types of  
7 malignancies or these types of lesions. I'm just asking you, the only way  
8 that you would say that we could have inherency is if say it was involved  
9 100 percent?

10 MS. DE LA PAZ: The standard that the Federal Circuit has set  
11 forth is necessarily present. You know, yes, while there may be some  
12 recognition by persons of ordinary skill in the art, the standard also requires  
13 that the missing descriptive limitation necessarily be present.

14 JUDGE LEBOVITZ: But isn't it necessarily present in that  
15 population? And didn't the Examiner satisfy his burden? Because he can't  
16 go out and get the data from Claimant and actually know whether, in fact -- I  
17 don't remember what numbers were being treated, or in the other  
18 references -- but isn't it enough that he's saying we know that 25, 90 percent  
19 of the population have it -- have HPV -- so therefore that's enough to sustain  
20 the Examiner's burden -- because the Patent Office doesn't have the facilities  
21 to go out and actually do the comparisons themselves. So from a burden  
22 standpoint, why isn't that enough?

23 MS. DE LA PAZ: Well, again, Clayman and the RAC meeting  
24 minutes were protocols. You know, they didn't describe actual data.  
25 Nevertheless -- regardless of that -- it's not enough, because inherent  
26 requires necessarily present. Otherwise, you would be trying to figure out,

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31 Appeal 2007-2864  
32 Application 10/747,798

1 well, where do you cut the line? Is it 5 percent Is it 50 percent Is it 80  
2 percent?

3 JUDGE GRIMES: Well, I think the line is one patient, right?  
4 If we knew that one patient had been treated as recited in this claim, we'd  
5 have a definite anticipation. Correct?

6 MS. DE LA PAZ: That's right. But we don't know. And that's  
7 the issue.

8 JUDGE GRIMES: But we know that the population is  
9 susceptible, and how could the Examiner ever make a case if he actually --  
10 hasn't the Examiner satisfied his burden by showing you that there's a factual  
11 probability?

12 MS. DE LA PAZ: No. He has not satisfied his burden. Out of  
13 the Mehl/ Biophile v. Milgraum case cited to In re Oelrich, which states that  
14 "inherency may not be established by probabilities or possibilities, and that  
15 occasional results are not inherent." So, that being said, appellants  
16 respectfully request that the Board reverse the rejections under 102  
17 pertaining to the RAC meeting minutes, Clayman, and Nielsen.

18 Now, just as far as a couple of dependent claims briefly,  
19 dependent claim 4 is additionally not anticipated by any of those rejections  
20 because dependent claim 4 recites, "wherein, the cell is a keratinocyte, and a  
21 keratinocyte is a cell that makes keratin. Oral mucosa and cervical mucosa  
22 are not lined by keratinocytes. The Examiner cites Flaitz as teaching that  
23 keratinocytes are squamous cells. While that may be true, it doesn't teach  
24 that Clayman, the RAC meeting minutes or Nielsen included keratinocytes.  
25 The oral cavity is not lined by keratinocytes.

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1 Now, as to claim 6, which recites, "wherein the cell is a skin  
2 cell," the Examiner argues that that claim is anticipated because he broadly  
3 argues that skin includes the lining of certain body cavities like the cervix  
4 and the mouth. However, the ordinary and customary meaning of terms, as  
5 you know, are evidenced by a variety of sources including the written  
6 description and claims and contrary to the Examiner's assertion, the ordinary  
7 and customary meaning of the term "skin" does not include mucosal tissues  
8 like the mouth or the cervix. As evidence, we cite to originally filed claim 6,  
9 which recites, "wherein the cell is a skin cell," and originally-filed claim 7,  
10 which recites, "wherein the cell is a mucosal cell." The fact that both claims  
11 depend from claim 1 supports the ordinary meaning, whereby, skin is  
12 distinct from mucosa.

13 JUDGE GRIMES: Why are those inconsistent with the  
14 Examiner's definition? They could just be dependent claims of different  
15 scope.

16 MS. DE LA PAZ: The Examiner argues that the claims are  
17 anticipated because the mouth is lined by skin, and we disagree. We argue  
18 for an ordinary and customary interpretation of skin that is distinct from  
19 mucosa of the mouth.

20 JUDGE GRIMES: I understand that. I'm just asking, do you  
21 have another basis for making that distinction, because I'm not really seeing  
22 that this necessarily supports your position.

23 MS. DE LA PAZ: Well, in our reply brief we cited to  
24 numerous places in the specification where we separately discuss skin versus  
25 mucosa, keratinocytes versus mucosa versus skin, and all those things



43 Appeal 2007-2864  
44 Application 10/747,798

1 support an ordinary interpretation such that skin does not encompass mucosa  
2 of the oral cavity or the lining of the cervix. If you'd like, I can go over this.

3 JUDGE GRIMES: I can look at it. If it's in the reply brief, I  
4 can find it.

5 MS. DE LA PAZ: So there's one additional rejection under  
6 102, which is not an inherent anticipation issue. The Examiner cites the  
7 El-Deiry reference as anticipating the claims. Now, El-Deiry discusses  
8 treatment of lesions that include papillomavirus-infected cells with a topical  
9 gene therapy using a viral vector that expresses p73, which is a different  
10 molecule than p53.

11 JUDGE GREEN: But El-Deiry specifically calls p73 a  
12 homolog of p53, correct?

13 MS. DE LA PAZ: El-Deiry does refer to P73 as a homolog of  
14 p-53. In our specification, we recite at page 14, lines 5 through 6,  
15 "throughout this application the term p-53 is intended to refer to the  
16 exemplified p53 molecules as well as all p-53 homologs from other species.  
17 So, stepping back, what do we mean by the exemplified p-53 molecules?

18 Well, one of ordinary skill in the art would have understood  
19 that from the specification that this is human p53. He or she would  
20 understand this to be the case because the section of the application where  
21 this definition appears addresses in detail the role of p53 in human cancer.  
22 And that's on pages 12 through 14 of the specification.

23 Indeed, the application is replete with reference to p-53, its role  
24 in human cancer and the role of human papillomavirus in human cancer. So,  
25 one of ordinary skill in the art would understand that if the exemplified p53  
26 molecule was a human p53, then in the context of the present specification,

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49 Appeal 2007-2864  
50 Application 10/747,798

1 the phrase, "all p53 homologs from other species refers to p53 molecules  
2 that are from non-humans, such as, for example, rat p53, mouse p53, dog  
3 p53, et cetera.

4 El-Deiry contains no disclosure pertaining to administration of  
5 any p53 molecules to any papillomavirus-transformed cell. Nor does it  
6 disclose any p53 molecule from another species. And we've set forth in a  
7 declaration from Dr. Louis Zumstein evidence to support an understanding  
8 that p53 in the present specification does not include p73, and that's Exhibit  
9 8 of the appeal brief.

10 Dr. Zumstein is a person of skill in the art with over 13 years of  
11 experience in the biotechnology field, and he has read through the  
12 specification, and it has declared that it is his belief that p73 is not homolog  
13 of p53.

14 JUDGE GRIMES: What is p73?

15 MS. DE LA PAZ: P73 is a molecule that is structurally  
16 different. It has some sequent similarities to human p53, but many sequence  
17 dissimilarities. It's not involved in carcinogenesis, per se. It's not involved  
18 in self-cycle growth.

19 If you look at our application, one of the areas of interest as to  
20 p53 was the fact that the E6 protein that's made by papillomavirus binds to  
21 p53 and causes degradation of p53. So our invention sought to administer  
22 p53 to correct that deficiency.

23 JUDGE GRIMES: But p73 presumably does not bind to E6.

24 MS. DE LA PAZ: P73 does not bind to E6. No. It does not. It  
25 does not undergo degradation.

26 JUDGE GRIMES: What does it do?

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55 Appeal 2007-2864  
56 Application 10/747,798

1 MS. DE LA PAZ: Pardon?

2 JUDGE GRIMES: What does it do?

3 MS. DE LA PAZ: I don't know, specifically. But anyway, all  
4 these things support our argument that p53 as set forth in our application  
5 does not include p73 of El-Deiry.

6 Now, the Examiner has cited to Kaghad as supporting his  
7 assertion that El-Deiry anticipates the claimed invention. Kaghad describes  
8 the sequence of p73, and again, while there might be some sequence  
9 similarity of p73 to p53, it makes clear in Kaghad that there are substantial  
10 sequence to similarities as well. Further, Kaghad specifically notes that "it is  
11 not obvious that p73 and p53 share common functions." This further  
12 supports appellants' position that p73 is not a homolog of p53 in the context  
13 of the present specification.

14 Further, regarding dependent claims, El-Deiry additionally does  
15 not anticipate claims 4, 6 or 6, because it does not disclose treatment of any  
16 keratinocyte or treatment of any skin cell.

17 Therefore, appellants respectfully request reversal of the  
18 rejection under 102 based on El-Deiry.

19 The last issue in this case pertains to a rejection under 103. The  
20 Examiner has argued that a subset of the claims are rendered obvious by the  
21 RAC meeting minutes in view of Oda and Flaitz, or El-Deiry in view of  
22 Zhang. Now, the Examiner has not met the Patent Office's burden of  
23 establishing a prima facie case of obviousness, because he has not shown  
24 that the cited combination of references provide any reasonable expectation  
25 of success to inhibit the proliferation of papillomavirus-infected cells.

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61 Appeal 2007-2864  
62 Application 10/747,798

1 Now, going back to the RAC meeting minutes, that was the  
2 minutes of a NIH committee meeting to discuss the Clayman protocol to  
3 administer intramucosal at p53 followed by oral swishes. Again, there's  
4 nothing in that reference that specifically sets forth any inhibition of the  
5 growth of a papillomavirus-infected cell. Oda and Flaitz, while they do  
6 make reference in their background sections to HPV-transformed cells, they  
7 don't provide any specific teaching or suggestion pertaining to gene therapy  
8 of papillomavirus-infected cells.

9 Oda actually is a reference that concerns chromosomal and  
10 cell-cycle changes in HPV-infected cells when grown and cultured. It does  
11 not even pertain to any in vivo studies or gene therapy. And Flaitz is a  
12 review article that concerns a discussion of virus infection and malignancies,  
13 and not gene therapy.

14 Further, as far as the El-Deiry reference just discussed, the fact  
15 that El-Deiry does not disclose p53 as the term p53 is discussed in the  
16 context of the present invention. It pertains to methods involving p73.  
17 Now, he combined Zhang with El-Deiry, but Zhang is only cited as teaching  
18 a flavirin, which is one of the limitations of some of the claims at issue.

19 Therefore, the Examiner hasn't established any reasonable  
20 expectation of success whatsoever that a person of ordinary skill when  
21 presented with the RAC meeting minutes and Oda and Flaitz, or El-Deiry  
22 and Zhang, would practice the claimed invention. Also, there's no prima  
23 facie case of obviousness, because there's suggestion or motivation to  
24 provide for the claimed invention based on these references. So he cites the  
25 Recombinant Advisory Committee meeting and El-Deiry as describing a

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67 Appeal 2007-2864  
68 Application 10/747,798

1 liquid delivery comprising an adenoviral vector to the mouth, and Zhang is  
2 teaching a flavorin.

3           However, the claims at issue are directed to inhibiting,  
4 suppressing, or preventing the growth of papillomavirus-transformed cells in  
5 a hyperplastic lesion, there's no specific motivation to provide for inhibiting,  
6 suppressing, or preventing the growth of a papillomavirus-transformed cell  
7 in a hyperplastic lesion using a flavorin composition that contains p53 in any  
8 of the references.

9           Quoting from In re Mills, a Federal Circuit case from 1990:  
10 "The mere fact that references can be combined or modified does not render  
11 the result and combination obvious unless the prior art also suggests the  
12 desirability of the combination. KSR also specifies that any analysis to  
13 argue that a suggestion in motivation must be made explicit, and here no  
14 such explicit analysis has been set forth.

15           So, in conclusion, in light of the above, none of the pending  
16 claims are properly rejected. Therefore, appellants respectfully request that  
17 the Board reverse the pending grounds for rejection.

18           JUDGE GRIMES: Any more questions?

19           JUDGE GREEN: No.

20           JUDGE GRIMES: Thank you, very much.

21           (Whereupon, at 2:06 p.m., the hearing was concluded.)  
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